relapse. Five pts have died (median 9 months), 2 from graft-versus-host disease (GVHD), 2 infections, and 1 elected Hospice care after experiencing renal failure. Last disease responses were complete remission (n = 8), partial remission (n = 6), stable disease (n = 5), not-evaluated (n = 1). The incidences of grades II and III-IV acute GVHD were 60% and 15% respectively, and chronic GVHD was 46% at 1-year. Estimated 1-year rate of non-relapse mortality (NRM), relapse, progression-free (PFS), and overall survivals (OS) were 33%, 0%, 67%, and 67% respectively. Patients receiving peri-HCT rituximab had lower HR for relapse (HR:0, p = 0.001), comparable HR for NRM (HR:1, p = 0.9) and OS (HR:0.7, p = 0.45), and a trend for lower HR for PFS (HR:0.5, p = 0.07) compared to the historical control group. At day 84, median CD3 chimerisms were 99% *vs* 95% (p = 0.08), respectively.

After adjusting for the previous 4 significant covariates, PFS was better (HR:0.4, p = 0.04) among the rituximab group. Peri-transplant rituximab is a promising addition to nonmyeloablative HCT and may decrease early disease progression by allowing the generation of potent GVL effects.

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LEUKEMIC TRANSFORMATION OF PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS: RESULTS OF A TREATMENT ALGORITHM EMPLOYING ALLOGENEIC TRANSPLANTATION USING RELATED AND UNRELATED DONORS

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Leukemic transformation (LT) is a rare but fatal complication of Philadelphia-negative myeloproliferative neoplasms (MPNs) for which optimal treatment strategies are not known. LT is generally considered incurable with induction chemotherapy alone.

At our centre, we have adopted a treatment strategy for LT where patients within the transplant age group who have a reasonable fitness level are offered induction therapy. Subsequently, those who achieve complete remission (CR/CRi) or revert back to a chronic MPN (cMPN) state are considered eligible for allogeneic transplantation (allo-SCT) if a suitable related or unrelated donor is available. Alternatively, those who are not candidates for the aforementioned strategy are offered supportive therapy including clinical trials.

We evaluated clinical outcomes of this treatment approach in 75 patients with LT diagnosed between 1998 and 2011. Prior to LT, MPN diagnoses were: PV, 16%; ET, 16%; primary MF, 28%; post-PV/ET MF, 25%; and MPN-U, 15%. 39 (52%) patients were treated with curative intent (induction chemotherapy +/- allo-SCT) while the remainder were treated with non-curative intent. At the time of LT, the curative intent cohort differed from the non-curative group in terms of median age (57 vs. 72 yrs, P<0.0001), performance status (ECOG≤1 in 92% vs. 58%, p = 0.001), serum albumin (38 vs. 35 g/L, p = 0.008) and the frequency of normal cytogenetics (47% vs. 20%, p = 0.03) respectively.

Among all patients, the 2-year overall survival (OS) from the time of LT was 15%. Outcomes were significantly improved in individuals treated with curative vs. non-curative intent (2-year OS, 25% vs. 4%, P< 0.0001). Among the curative group, 30/39 achieved either CR (n = 19) or reversion to cMPN (n = 11). Suitable donors were identified for 24 (80%) of these responders and 17 (57%) underwent allo-SCT. Median time to transplant was 177 days. Survival of patients undergoing allo-SCT was significantly better compared to those who achieved CR/cMPN post-induction but were not transplanted (2-year OS, 46% (n = 17) vs. 15% (n = 13), P = 0.035). To avoid a time to transplant bias, a landmark analysis was done comparing survival between the transplant cohort and non-transplanted patients who survived at least 177 days (n = 13), and similar results were observed (2-year OS 46% vs. 15%, p = 0.035).

Our results demonstrate the curative potential of intensive induction therapy followed by allo-SCT in select patients with LT preceded by MPN.

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LOW DAY 100 TRANSPLANT-RELATED MORTALITY (TRM) FOLLOWING CLOFARABINE (CLO) IN COMBINATION WITH CYTARABINE AND TOTAL BODY IRRADIATION (TBI), MYELOABLATIVE CONDITIONING (MAC) AND ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS (CAYA) WITH POOR-RISK ACUTE LEUKEMIA

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Background: CAYA with ALL or AML in third complete remission (CR3), refractory relapse (RR) or induction failure (IF) have an extremely poor prognosis, <20% EFS (Gaynon, BJH, 2005, Wells et al, JCO, 2003). MAC prior to AlloSCT is associated with high TRM and is donor dependent: 5-20% for matched sibling, 10-40% for matched unrelated, and 20-52% for cord blood transplants. CLO, an inhibitor of DNA polymerase and ribonucleotide reductase, has been shown to be safe and induce durable remissions, both in conjunction with busulfan in poor-risk AML (Magenau et al., Blood, 2011) and with Melphalan in poor-risk hematologic malignancies in adults (van Besien et al, ASH,2009). CLO has significant activity in CAYA with relapsed ALL/AML (Jeha et al., JCO 2006,2009) and synergy with cytarabine (Faderl et al, Blood, 2005). We sought to determine safety, day-100 TRM, and overall survival (OS) of CLO, cytarabine and TBI followed by AlloSCT in CAYA with poor-risk ALL/AML.

Methods: This is an ongoing multi-center phase I/II trial of a novel conditioning regimen of CLO (dose escalation: 40mg/m^2 [n = 3], 46 mg/m^2 [n = 3], 52 mg/m^2 [n = 17]) x5d, sequential (4 hrs later) cytarabine 1000 mg/m^2 x6d and TBI (1200cGy) followed by AlloSCT from matched related or unrelated donors in CAYA with ALL/AML in CR3, RR or IF. Pts with unrelated grafts received R-ATG. GVHD prophylaxis consisted of tacrolimus and MMF (Bhatia/Cairo et al., BBMT, 2009). Kaplan-Meier method was used to determine the probabilities of engraftment, GVHD, TRM and OS.

Results: 23 pts, median age: 10.8 yrs (1.5-20.7); M:F: 17:6, ALL/AML: 20:3 (9 CR3, 3 RR, 11 IF), 9 related donors, 14 unrelated donors (8 BM/PBSCs, 6 UCB). Median TNC and CD34 dose was 4.76x10^8/kg and 4.84x10^6/kg for BM/PBSCs and 4.0x10^7/kg and 2.8x10^5/kg for UCB, respectively. Probabilities of neutrophil and platelet engraftment and grade II-IV aGVHD were 100%, 92.8% and 50.8%, respectively. All except one achieved 100% whole blood donor chimerism by day 30. CLO dose was tolerable at 52mg/m^2/d x5d without dose limiting toxicity. Probability of Day 100 TRM was only 5%. Probability of 1-yr PFS and OS were 45% (CI_{95}: 24-83%), and 44.6% (CI_{95}: 24-68%) respectively.

Conclusions: Preliminary results suggest this novel MAC regimen followed by AlloSCT is safe and well tolerated in CAYA with poor-risk ALL/ AML with CLO dose of 52 mg/m^2. Early results are encouraging with respect to low risk of day 100 TRM with this conditioning regimen in this poor-risk population.

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OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): IMPACT OF MYELOABLATIVE (MA) VS. REDUCED-INTENSITY CONDITIONING (RIC) REGIMENS, AND IMPACT OF TOTAL BODY IRRADIATION (TBI)-BASED MA VERSUS CHEMOTHERAPY (CT)-BASED MA CONDITIONING

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There has been a marked change in transplant approaches of the CLL patient. MA conditioning has been shown to provide high

complete remission (CR) rates and long-term survival, however, it remains associated with significant treatment related mortality (TRM) and it remains unclear whether a CT - or TBI-based MA regimen is most efficacious. RIC has also been shown to achieve durable long-term survival with a lower TRM (15-25%) and has been generally used for older patients. To attempt to compare these procedures an analysis of CLL patients undergoing first Human Leukocyte Antigen (HLA)-matched sibling donor (MRD) HCT between 1995 and 2007 was performed, focusing on differences between: 1) MA vs. RIC transplants; and 2) CT- vs. TBI-based MA conditioning.

Among 297 patients, 163 MA vs. 134 RIC, significant differences in baseline characteristics included: Median age; source of stem cells; median donor age; use of antithymocyte globulin (ATG); graft versus host disease (GVHD) prophylaxis; and the year of transplantation. Multivariate analysis demonstrated that MA conditioning was associated with a higher incidence of acute GVHD ($p = 0.002$) and a higher TRM ($p = 0.003$), but a lower relapse rate ($p = 0.005$). Although there was no difference in survival before year 2000, after year 2000, MA conditioning was associated with reduced survival by almost 2-fold ($p = 0.019$).

Among 163 patients who had MA conditioning, 110 were TBI-based and 53 were CT-based. Significant differences in baseline characteristics were: Rai stage at diagnosis, stem cells source, and the use of ATG (0 vs. 11%, $p<0.001$). As compared to the CT-based transplants those with TBI tended to be performed earlier with the majority being before year 2000 ($p = 0.052$). Although there were no significant differences between the groups regarding GVHD, neutrophil engraftment, relapse or survival, the CT-based conditioning group had higher TRM ($p = 0.006$) and treatment failure risk.

We conclude from this large retrospective comparison that RIC HCT from a MRD is effective in an older CLL population with superior survival and less TRM than that observed with MA conditioning. However, due to the higher relapse rate in the RIC group, future strategies to enhance the anti-leukemic effect are warranted. In the MA setting, TBI-based conditioning may be superior to a CT-based approach; however, recognizing the emerging efficacy of RIC HCT, a prospective comparison is unlikely to be performed.

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PRECLINICAL MODEL TO PREDICT ANTI-LEUKEMIC ACTIVITY OF BUSULFAN AND IRRADIATION

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We tested the in vitro effect of physiologic doses of busulfan (Bu) and ionizing radiation (IR) to address whether additive antileukemic activity can be demonstrated in two leukemic cell lines, one sensitive (HL60) and one resistant (K562) to radiation. Cells were treated for 24 hours with Bu doses ranging from at 0 to 200 μg/ml, or IR at 1.5, 3 or 6 Gy, or with BU at 12.5 or 25 μg/ml for 24 hours, followed by IR at 1.5 or 3Gy. Cells were then tested for proliferation, expression of annexin-V and caspase-3, and colony formation. Exposure to Bu or IR induced a variable but dose dependent inhibition of proliferation and colony formation in HLA-60 cells. On the contrary, we could observe a significant cytotoxic effect in K562 cells by using IR at 6, but not 1.5 or 3.0 Gy ($p = 0.008$). In addition, treatment with either Bu or IR caused apoptosis with increased caspase-3 expression in HL60 cells, but not in K562 cells. To test a possible synergistic effect of the combination of Bu and IR, we treated the cells with Bu for 24 hours followed by radiation. HL60 cells were strongly inhibited by both agents when separate or combined. In contrast, treatment of K562 cells with low dose IR (3Gy) alone inhibited colony formation by 28% and with low dose Bu by 77%. The inhibitory effect of low dose Bu + IR 3Gy increased up to 86%, suggesting that Bu could induce radio-resistant leukemic cells to become more radio-sensitive. In order to identify genes associated with a response to Bu, we formed a linear regression model controlled for cancer type using GI_{50} and Stanford cDNA array data from the NCI-60. 7 genes were identified that strongly correlated with response ($p<0.001$ and FDR ~50%). The most significant genes were then tested in the Affymetric U133 plus 2.0 platform. Our analysis identified six genes (ERC2, HCLS1, CD74, KCNH2, HLADQB2, CD53) which are significantly associated with response to Bu ($p<0.05$). Our in-vitro study demonstrated an additive effect of Bu and low dose IR even on radioresistant leukemic cells. The identification of a genomic signature for response to Bu validated by in vitro functional assays represents a novel approach for a personalized chemo-radiotherapy in patients with AML undergoing an allogeneic stem cell transplant.

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TARGETING LEUKEMIA BY CD123 SPECIFIC CHIMERIC ANTIGEN RECEPTOR

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Chimeric antigen receptors (CARs) are employed to genetically modify T cells to redirect their specificity to target antigens on tumor cells. Typically a second generation CAR is derived by fusing an extracellular domain derived from the scFv of monoclonal antibody (CAR) specific to targeted antigen with CD3ζ, and CD28 endodomains. CD123 (IL3RA) is expressed on 45% to 95% of acute myelogenous leukemia (AML) and B-cell lineage acute lymphoblastic leukemia (B-ALL). Expression of CD123 is high in the leukemic stem cell (LSC) population, but not in normal hematopoietic stem cells. Thus, CD123 appears to be potential target for immunotherapy in leukemias through chimeric antigen receptor (CAR). We hypothesized that the generation of CD123 specific CAR can redirect the specificity of T cells to CD123 and this was tested by cloning the scFv of CD123 mAb in our CAR construct. The sleeping beauty system was used to express the CAR and DNA plasmids were electroporated into peripheral blood mononuclear cells and cells were numerically expanded on artificial antigen presenting cells genetically modified to express co stimulatory molecules CD86, 4-1BBL, membrane-bound IL-15, and CD123 antigen in presence of IL-21 and 1L-2. CAR+ T numerically expanded to clinically relevant numbers and showed antigen specific cytotoxicity in leukemic celllines. CAR+ T cells expressed both effector and memory markers showing the potential for ***in vivo*** persistence after T cell infusion. The bone-marrow homing receptor CXCR4 was expressed by CAR T cells shows the potential to target LSC that reside in BM niches. The preliminary data suggests that mirroring an approach we are using to manufacture clinical grade CD19 specific CAR+ T cells.

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INCREASED ABILITY TO TRANSPLANT AND IMPROVED SURVIVAL IN PATIENTS WITH HIGH RISK ACUTE MYELOID LEUKEMIA (AML) AFTER INDUCTION WITH HIGH DOSE CYTARABINE AND MITOXANTRONE (HIDAC/MITO)

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Background: Patients with high risk AML have a poor prognosis and inferior outcomes after 7+3 induction. Complete remission (CR) rates range from 6-51% and induction death rates between 9-48%. We present a single institution experience in high risk AML patients treated with HIDAC/MITO induction regimen (Blood 2010; 116: 3290).

Methods: We have retrospectively analyzed the outcome of 43 patients with AML who received HiDAC/MITO induction at our institution from January 2009- September 2011. High risk features included at least one of the following such as age>60, high risk cytogenetics, high age adjusted Charlson comorbidity index (CCI) and non denovo AML (therapy related, antecedent hematological disorder or relapsed AML). The endpoints analysed were CR (marrow blasts <5%) at day 30, induction mortality within 30 days of induction, ability to proceed to transplant, number of days to transplant, overall survival (OS) and progression free survival (PFS) of transplanted vs non transplanted patients, calculated from day 1 of induction.

Patient characteristics: The median age was 67 years (47 - 83), median age adjusted CCI was 6 (4 -12), 26 (60%) were males and 17